POLICY: Transplantation – Nulojix® (belatacept for intravenous infusion – Bristol-Myers Squibb)

DATE REVIEWED: 07/24/2019

OVERVIEW

Nulojix is a soluble fusion protein indicated for prophylaxis of organ rejection in adult patients receiving a kidney transplant.[1] Nulojix is to be used in conjunction with basiliximab, mycophenolate mofetil, and corticosteroids. Nulojix works by selectively blocking T lymphocyte costimulation by binding to CD80 and CD86 on antigen presenting cells thus inhibiting CD28 mediated activation of T lymphocytes. This results in a reduction of T lymphocyte cytokines which are needed for the development of antigen-specific antibodies by B lymphocytes.

Note. The prescribed dose must be evenly divisible by 12.5 mg.[1] Use of higher than recommended doses or more frequent administration is not recommended due to the increased risk of post-transplant lymphoproliferative disorder (PTLD) predominately of the central nervous system (CNS), progressive multifocal leukoencephalopathy (PML) and serious CNS infections. The dose is based on actual body weight of the patient at the time of transplantation and should not be modified during the course of treatment unless the patient's weight changes by > 10%.

Guidelines

Nulojix is not included in the guidelines. In 2009, the Kidney Disease Improving Global Outcomes (KDIGO) published clinical practice guidelines for the care of kidney transplant recipients.[2] The guidelines are extensive. For maintenance therapy, it is recommended to employ a combination of immunosuppressive medications including a calcineurin inhibitor and an anti-proliferative agent, with or without corticosteroids. Compared to cyclosporine, tacrolimus reduces the risk of acute rejection and improves graft survival within the first year of transplantation. Tacrolimus is the first-line calcineurin inhibitor and it is suggested that tacrolimus (or cyclosporine) be initiated before or at the time of transplantation, rather than delayed until the onset of graft function. Mycophenolate should be used first-line as an anti-proliferative agent. Patients who are at low immunological risk and who receive induction therapy should have corticosteroid therapy discontinued during the first week post-transplantation. If a mammalian Target of Rapamycin (mTOR) inhibitor (Zortress® [everolimus], Rapamune® [sirolimus]) is used, it should not be commenced until graft function is established and surgical wounds are healed. In the case of no reported acute rejection, the lowest doses of maintenance immunosuppressive medications should be maintained two to four months post-transplant. Calcineurin inhibitors should be continued. Of note, many of the mediations require the monitoring of levels (e.g., calcineurin inhibitor, mycophenolate mofetil, mTOR inhibitors).

Safety

Nulojix labeling contains a boxed warning for PTLD; other malignancies and serious infections; and use in liver transplant recipients.[1] Patients receiving Nulojix are at increased risk of developing PTLD, particularly those without immunity to the Epstein-Barr virus (EBV). Nulojix should only be used in individuals who are EBV seropositive, do not use in individuals who are EBV seronegative or with unknown EBV status. Individuals receiving Nulojix are at increased risk of developing infections or malignancies due to immunosuppression. Nulojix should not be used in liver transplant recipients due to an increased risk of graft loss and death.

Liver Transplantation

Nulojix has a boxed warning stating that use in liver transplant recipients is not recommended due to an increase risk of graft loss and death.[1]

In a partially-blinded, active-controlled, parallel group, Phase II trial (N = 260), patients receiving the first liver transplant were randomized 1:1:1:1:1 to basiliximab + Nulojix high-dose + mycophenolate mofetil; or Nulojix high-dose + mycophenolate mofetil; Nulojix low-dose + mycophenolate mofetil; tacrolimus + mycophenolate mofetil; or tacrolimus alone.[3] The primary endpoint was the composite of acute rejection, graft loss and death at 6 months. Secondary endpoints included the incidence, severity, treatment and outcome of acute rejection at 12 months; graft loss and death at 12 months; and change in renal function over time. At 6 months, the frequency of the composite endpoint was higher in the Nulojix groups (42% to 48%) compared to the tacrolimus groups (15% to 38%), driven mostly by a higher rate of acute rejection with Nulojix. An external Data Monitoring Committee stopped further enrollment in the Nulojix low-dose arm due to an increase in graft loss and death compared to the other arms of the study, however patients already on Nulojix low-dose were allowed to continue at the discretion of the investigator. At 12 months, there was a higher rate of acute rejection and death in the Nulojix groups compared to tacrolimus + mycophenolate mofetil. The long-term extension phase was terminated early when the Data Monitoring Committee determined there was continued graft loss and death in the Nulojix high-dose group.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Nulojix. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by an Express Scripts clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Nulojix as well as the monitoring required for adverse events and long-term efficacy, approval requires Nulojix to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

1. **Kidney Transplantation – Prophylaxis of Organ Rejection.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** The patient is ≥ 18 years of age; AND
   - **B)** The patient is Epstein-Barr virus (EBV) seropositive; AND
   - **C)** Nulojix is prescribed by or in consultation with a transplant specialist physician or a physician associated with a transplant center.

   Dosing. Approve the following dosing regimen (A and B):
   - **A)** Each individual dose must not exceed 10 mg/kg administered by intravenous infusion; AND
   - **B)** Nulojix is administered no more than four times in the first 4 weeks (day of transplant, Day 5, end of Week 2, and end of Week 4), and then no more frequently than once every 4 weeks.[1]

Other Uses with Supportive Evidence

2. **Solid Organ Transplantation Other Than Kidney – Prophylaxis of Solid Organ Rejection in a Patient Currently Receiving Nulojix.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** The patient is ≥ 18 years of age; AND
   - **B)** The patient is Epstein-Barr virus (EBV) seropositive; AND
   - **C)** Nulojix is prescribed by or in consultation with a transplant specialist physician or a physician associated with a transplant center.

   Dosing. Approve the following dosing regimen (A and B):
   - **A)** Each individual dose must not exceed 10 mg/kg administered by intravenous infusion; AND
   - **B)** Nulojix is administered no more than four times in the first 4 weeks (day of transplant, Day 5, end of Week 2, and end of Week 4), and then no more frequently than once every 4 weeks.[1]

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Nulojix has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Nulojix® for injection [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; April 2018.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. *Am J Transplant*. 2009;9(Suppl 3):S1 – S157. Accessed on 7/2/2018 at: https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2009-Transplant-Recipient-Guideline-English.pdf.
3. Klintmalm GB, Feng S, Lake JR, et al. Belatacept-Based Immunosuppression in *De Novo* Liver Transplant Recipients: 1-Year Experience From a Phase II Randomized Study. *Am J Transplant*. 2014;14:1817-1827.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	--	08/15/2018
Annual	Removed Patient Currently Receiving Nulojix criteria from Kidney Transplant indication. Added criteria to Solid Organ Transplant Other Than Kidney to allow patients already started on Nulojix who meet the criteria to continue receiving Nulojix. Removed Waste Management, Initial Approval/Extended Approval, Duration of Therapy, and Labs/Diagnostics sections.	07/24/2019

* For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; TAC – Therapeutic Assessment Committee;